INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

EFFICACY

Released for Consultation

at *Step 2* of the ICH Process

on 20 July 2000

by the ICH Steering Committee

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

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Draft ICH Consensus Guideline

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CLINICAL OVERALL SUMMARY

The Clinical Overall Summary (COS) is intended to provide a critical analysis of the clinical data in the Common Technical Document. The COS will necessarily refer to application data provided in the comprehensive Written Summary of Clinical Studies and Experience, the individual clinical study reports (ICH E3), and other relevant technical reports. But it will primarily present the conclusions and implications of those data, and will not recapitulate them.

This document is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. It is intended to be a concise analysis of information pertinent to the clinical use of the pharmaceutical, including reference to relevant information from the quality and safety sections of the application. This document should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the pharmaceutical in its intended use, and describe how the study results support critical parts of the prescribing information. In order to achieve these objectives the Clinical Overall Summary (COS) should:

- describe and explain the overall approach to the clinical development of a pharmaceutical, including critical decisions (e.g., study endpoints, subject selection criteria, choice of controls)
- provide a brief overview of the clinical findings, including important limitations (e.g. absence of information on some patient populations), pertinent endpoints or combination use,
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies and an evaluation of how prescribing information and other approaches will optimise benefits and minimise risks,
- address particular efficacy or safety problems encountered in development, and how they have been evaluated and resolved,
- explore unresolved issues, explain why the sponsor believes they should not be considered as barriers to regulatory approval, and describe plans to resolve them.
- explain the basis for important or unusual aspects of the prescribing information (package insert, Summary of Product Characteristics).

The COS will generally be a relatively short document (about 30 pages). The 30 page recommendation is a target but is not mandatory. The size will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged, in order to facilitate brevity and understanding. The COS should include discussion of the following topics:

- Product Development Rationale
- Overview Analysis of Biopharmaceutics
- Overview Analysis of Clinical Pharmacology
- Overview Analysis of Efficacy
- Overview Analysis of Safety
- Benefits and Risks
- References

1. PRODUCT DEVELOPMENT RATIONALE

The discussion of the rationale for the development of the pharmaceutical should:

- identify the pharmacological class of the pharmaceutical.
- describe the particular clinical/pathophysiological aspect of the disease process that the pharmaceutical is intended to treat (the targeted indication).
- briefly summarize the scientific background that supported the investigation of the medicine for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the pharmaceutical
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies (e.g., use of a different efficacy scale, use of a novel study design, absence of formal dose finding studies). Pertinent regulatory guidance or advice should be identified.

2. OVERVIEW ANALYSIS OF BIOPHARMACEUTICS

The purpose of this section is to describe and analyse important issues related to drug formulations that might affect efficacy and/or safety of the to-be-marketed formulations (e.g. polymorphism of drug substance, dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure [Cmax and AUC], lot-to-lot variability).

3. OVERVIEW ANALYSIS OF CLINICAL PHARMACOLOGY

The purpose of this section is to present a critical analysis of the pharmacokinetic, pharmacodynamic and in vitro metabolism data in the CTD. It should emphasize unusual results and known or potential problems, or note the lack thereof. This section should provide evidence for specific prescribing information addressing:

- Pharmacokinetics, e.g., comparative pharmacokinetics in healthy subjects, patients, and special populations; pharmacokinetics related to intrinsic factors (e.g., age, sex, race, renal and hepatic failure) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including possible genetic

polymorphism and the formation of active and inactive metabolites; stereochemistry issues; clinically relevant pharmacokinetic interactions with other pharmaceuticals or other substances.

- Pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e. PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant pharmacodynamic interactions with other pharmaceuticals or substances.
- Special product features, e.g., immunogenicity; clinical microbiology

4. OVERVIEW ANALYSIS OF EFFICACY

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the pharmaceutical product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be discussed:

- relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly. Any differences between the studied population(s) and the population that would be expected to receive the pharmaceutical after marketing should be discussed.
- appropriateness of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Any reliance on endpoints that have not previously been used as a basis for approval should be discussed.
- statistical methods and any issues that could affect the interpretation of the study results (e.g., support for any unplanned analyses; interpolation of data for discontinuations and corrections for multiple endpoints).
- similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data. Identify sub-groups for which data are insufficient to reach conclusions.
- observed relationships between efficacy and dosage regimen for each indication in the total population and in the different patient subgroups.
- support for the applicability to the new region of data generated in another region, if necessary (ICH E5).
- for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Support for the chosen duration of the trials should be provided. Development of tolerance should be considered.
- data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma range.
- the clinical relevance of the magnitude of the observed effects. .

- for non-inferiority trials used to establish efficacy, the evidence supporting a determination that the trial had assay sensitivity and the basis of the choice of non-inferiority margin (ICH E10).
- efficacy in special populations. If efficacy is claimed without clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

5. OVERVIEW ANALYSIS OF SAFETY

The purpose of this section is to provide a concise critical review of the safety data, noting how results support and justify proposed prescribing information. A critical assessment of relative safety should consider:

- experience of the pharmacological class, particularly any unusual toxicities. Approaches taken to monitor for similar effects should be described.
- special approaches to monitor particular toxicities (e.g.. ophthalmic, QT prolongation).
- relevant animal toxicology and product quality information. Any findings that impact or could potentially impact the evaluation of safety in clinical use should be described. Any clinical data specifically collected to address potential risks should be discussed.
- patient population in the safety analyses. The total patient population included in the safety evaluation should be described (number, duration, dose, exposure in special populations, exposure in patients with risk factors).
- common and non-serious adverse events with reference to the tabular presentations in the Written Summary. The discussion should be brief, focusing on events of relatively high frequency and on those with an incidence higher than placebo or active controls. Any important considerations for the prevention, mitigation or management of these adverse events should be noted.
- serious adverse events (relevant tabulations should be cross-referenced from the Written Summary). This section should discuss the absolute number and frequency of serious adverse events, including all deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification). Any conclusions regarding causal relationship (or lack of this) to the product or dose-response relationships should be provided. In addition, the discussion should consider the following:
  - any differences in serious adverse events in population subgroups..
  - analyses, conclusions, and recommendations regarding the identification of risk factors for serious adverse events.
  - methods to prevent or ameliorate the severity of events.
  - laboratory findings reflecting actual or possible serious medical effects..
- reactions due to overdose, the potential for dependence and rebound phenomena.
- world-wide marketing experience. The following should be briefly discussed:
  - the extent of the world-wide experience,
  - any new or different safety issues identified

- any regulatory actions related to safety.

6. BENEFITS AND RISKS

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the pharmaceutical and to provide an overall appraisal of the benefits and risks of its use in clinical practice. This assessment should provide a clear basis for the proposed Prescribing Information. This section should also consider the risks and benefits of the pharmaceutical as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option. The analyses provided in previous sections should not be reiterated here and this section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class. This section should provide an integrated discussion of the benefits and risks of the pharmaceutical.

The format and content of this discussion of the benefits and risks of the pharmaceutical will depend greatly on the characteristics of the illness being treated, the observed therapeutic effects, the anticipated risks of the pharmaceutical, and differences between the pharmaceutical and other currently available treatments. However, this analysis of benefits and risks should generally consider the following points:

- the efficacy of the pharmaceutical, as determined in well-defined study populations for each proposed indication.
- significant safety findings, including common adverse events and serious adverse events associated with use of the pharmaceutical, and any measures that may enhance safety.
- dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
- efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity and organ function.
- any risks to the patient of known and potential clinically significant interactions, including food-drug and drug-drug interactions, and appropriate recommendations for product use.
- any risks associated with polymorphic metabolism
- any potential effect of the pharmaceutical on the patient's activity that could place him at risk, e.g., risk of driving or operating heavy machinery due to drowsiness.
- the anticipated risks and benefits of the product in clinical use, with consideration of variations in clinical practice patterns and available alternative treatments.
- any plans for post-marketing studies (optional).

9. REFERENCES

A list of references used, in addition to those contained in the dossier, should be given and stated in accordance with 1979 "Vancouver Declaration" on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", or the system used in "Chemical Abstracts."

WRITTEN SUMMARY OF CLINICAL STUDIES AND EXPERIENCE

TABLE OF CONTENTS

1. SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

1.1 Background and Overview

This section provides the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), bioequivalence (BE), and in vitro dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision)

1.2 Summary of Results of Individual Studies

A brief, narrative description of each of the individual studies that provide important in vitro or in vivo data and information relevant to BA and BE should be presented. The narrative descriptions should provide enough detail about the study objectives, study design and conduct, data analysis, and important results to allow the reviewer to understand what the study questions were, what was done to address them, what data were collected and analyzed, and what the major outcomes were. These narratives should be consistent with and may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

1.3 Comparison and Analyses of Results Across Studies

This section provides a factual summary of the *in vitro* dissolution, BA, and BE properties of the drug and drug product in all studies that were carried out, with particular attention to differences in results across studies. This overview should consider the following:

- evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and BE. When manufacturing or formulation changes are made for complex drug products (e.g. a protein product,), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported as BE studies in this section.
- evidence of the extent of food effects on BA and BE with respect to meal type or timing of the meal (where appropriate).
- evidence of correlations between *in vitro* dissolution and BA and BE.
- proportionality of BA and BE of different dosage form strengths.
- comparison between single and repeated-dose BE.
- BE of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- the source and magnitude of observed inter- and intrasubject variability in BA and BE measurements, e.g., area under the concentration-time curve (AUC) and peak concentration (Cmax).

Section 1 Appendix

Tables 1.1 and 1.2 are provided as examples of tabular formats for reporting information and results related to *in vitro* dissolution and bioavailability studies respectively. Tables prepared for reporting the results of bioequivalence studies would also include the mean ratios (test/reference) for Cmax and AUC and their 90% confidence interval.

These tables are not intended to be templates, but only to illustrate the type of information that should be considered by a sponsor in designing their own tables for biopharmaceutic studies. Sponsors should also decide whether information and results from these studies are best presented in tables, text or figures in order to aid clarity.

2. SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.1 Background and Overview

This section provides the reviewer with an overall view of the clinical pharmacology studies. These studies include those performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and the in vitro studies performed with human biomaterials pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarized in sections 1, 3 and 4 may also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterise PK and PD of the pharmaceutical, including studies of PK/PD relationships in healthy subjects and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships[1]. Critical aspects of study design and data analysis should be noted, e.g., the choice of the single or multiple doses used, the study population, choice of the intrinsic or extrinsic factors that were studied, the choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyze data to assess PK or PD.

2.2 Summary of Results of Individual Studies

A brief, narrative description of each of the critical individual studies that provide in vitro or in vivo data and information relevant to PK, PD and PK/PD relationships should be presented. The ICH E3 synopses of the individual studies should be included collectively in section 5 of this written summary document.

The narrative descriptions should provide enough detail about the study objectives, study design and conduct, data analysis, and important results to allow the reviewer to understand

[1] In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

what the study questions were, what was done to address them, what data were collected and analyzed, and the major outcomes

References or electronic links to the full report of each study should be included in the narratives.

Note that summaries of human dose-response pharmacokinetic and PK/PD studies intended to establish dose range for the targeted indication are to be included in this section. These studies will be of relatively short duration. In some cases, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy, they should be placed in the Summary of Clinical Efficacy section and referenced, but not summarized here.

2.3 Comparison and Analyses of Results Across Studies

This section uses the results of all *in vitro* human biomaterial studies and PK, PD and PK/PD studies to characterise the PK, PD and PK/PD relationships of the drug. Results related to the inter- and intra-individual variability in these data and the intrinsic and extrinsic factors affecting these pharmacokinetic relationships should be discussed.

This section should provide a factual presentation and discussion of all data across studies that address the following:

1) Results of *in vitro* drug metabolism and *in vitro* drug-drug interaction studies and their clinical implications.
2) All data from human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualization in the target patient population and in special populations, e.g., pediatric or geriatric patients, or patients with renal or hepatic impairment.
3) Results of any population PK analyses, such as results based on sparse sampling across studies that address inter-individual pharmacokinetic variations in the PK or PD of the active drug substances that may be due to extrinsic or intrinsic factors.
4) Dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the pivotal clinical trials. In addition, information that supports the dosage instructions in the final labelling should be discussed in Section 3.3.4.
5) Any major inconsistencies in the human biomaterial, PK, or PD database and any areas needing further exploration.
6) Any bridging studies that use pharmacological endpoints and that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the study and analysis of the similarity of pharmacological data between regions or races should be summarized in this section. An independent subsection can be created to summarize these kinds of data.

2.4 Special Studies

This section is for studies that provide special types of data relevant to specific types of pharmaceuticals. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarised here. Any observed or potential effects on PK, PD, safety and/or efficacy should

be considered in the appropriate section of the Written Summary as well, with cross-referencing to this section.

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarized in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data may be described in the efficacy section. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarized; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre, timing of onset and duration of antibody responses should be summarized for each type of antibody assay used (e.g., IgG by ELISA, neutralization). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarized. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analyzed and summarized.

It is particularly important to summarize analyses of potential clinically relevant correlates of immunogenicity, e.g., to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology

For antimicrobial or antiviral pharmaceuticals, in vitro studies to characterise the spectrum of activity are an important part of the programme of studies relevant to clinical efficacy. Clinical efficacy studies that include characterisation of the susceptibility of the clinical isolates as a part of the efficacy determination would be included in Section 3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of in vitro susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

Section 2 Appendix

Table 2.1 is provided as an example of a tabular format for reporting information and results related to pharmacokinetic studies. This table is not intended to be a template, but only to illustrate the type of information that should be considered by a sponsor in designing their own tables. Sponsors should also decide whether information and results from clinical pharmacology studies are best presented in tables, text or figures in order to aid clarity.

In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, sponsors should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

- Metabolism studies of pharmaceutical using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution and relevant kinetic parameters (e.g., Vmax, Km).
- Drug-drug interactions of pharmaceuticals using human biomaterials: for studies of other drugs inhibiting the new pharmaceutical, include metabolite inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_I values and proposed mechanism of inhibition. For studies of the new pharmaceutical inhibiting other drugs, include the drugs and metabolites inhibited along with the information mentioned above.
- Population PK studies: co-variates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (+ sd) PK parameters.

3. SUMMARY OF CLINICAL EFFICACY

A separate Section 3 should be provided for each indication, although closely related indications may be considered together. When more than one Section 3 is submitted, the sections should be labeled 3A, 3B, 3C, etc.

3.1 Background / Overview of Clinical Efficacy

This section describes the program of controlled studies and other pertinent studies in the application that evaluated efficacy. Controlled studies include studies with historical or other external control groups, as well as studies with placebo, no-treatment, dose-response, and active control groups. Any of these results that are pertinent to evaluation of safety should be discussed in Section 4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, e.g., randomization, blinding, choices of control treatment, choice of patient population, study endpoints, study duration, unusual design features such as crossover or randomized withdrawal designs, use of run-in periods, and other methods of "enrichment". Although this section is intended to focus on clinical investigations, preclinical data and clinical pharmacological data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy.

3.2 Summary of Individual Clinical Efficacy Studies

A brief narrative description for important studies should be presented. The narrative descriptions should provide enough detail about the study objectives, study design and conduct, data analysis, and critical results to allow the reviewer to understand what the study questions were, what was done to address them, what data were collected and analyzed, and what the major outcomes were. These narratives should be consistent with and may be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

3.3 Comparisons and Analyses of Results Across Studies

This section presents all available data that characterize the efficacy of the drug. This section should cross-reference data from all studies designed to evaluate the efficacy of the drug. This summary will include analyses of all data, irrespective of their support for the overall

conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilize two kinds of analyses: comparison of results of individual studies, and/or analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Module V, Section 5.3.

This section should also cross-reference important evidence from section 2, such as data that support the dosage and administration section of the labeling. These data include dosage and dose interval recommended, evidence pertinent to individualization of dosage and need for modifications of dosage for specific subgroups (e.g., pediatric or geriatric subjects, or subjects with renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

3.3.1 Study Populations

The demographic and other baseline characteristics of patients across all studies should be described. The following should be included :

- the characteristics of the disease (severity, prior treatment, duration) in the patients studied and any limitations on conclusions imposed by the inclusion/exclusion criteria.
- the adequacy of follow-up and the number of patients who dropped out. The reasons why the patients did not complete the study and the times (after initiation of therapy) when the patients were withdrawn or lost to follow up should be summarized.
- differences in baseline characteristics of the study populations in different studies or groups of studies. Any impact of such differences on the results should be discussed.
- any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.

Tabular presentations that combine and compare study populations across studies may be useful.

3.3.2 Comparison of Results of all Clinical Efficacy Studies

The results from all studies designed to evaluate the drug's efficacy should be summarized and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, statistical methods, patient population, and dose should be identified. In general, studies with different controls (placebo, active) should be discussed separately.

If many variables or time points were analyzed, it may be useful to select representative data for display in comparisons. If results over time are critical, results of many studies over time can be displayed in a single figure, e.g. displaying difference from control with confidence intervals for the difference, using a separate line for each study. Confidence intervals for the treatment effects should always be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo, should

generally be presented in the table or in text accompanying a figure. If the objective of an active control trial was to show equivalence or non inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or non inferiority with the rationale for the criteria provided (see ICH E10). Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to predefined protocol criteria or is a post hoc exercise, and appropriate statistical adjustments should be discussed. Any source of bias related to differences between subject populations or differences in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (section 5.3 of Module V).

3.3.3 Analyses of Demographic Subsets and other Covariates

The results of individual studies or overview analyses of efficacy in specific populations, e.g., the elderly, or in specific disease stages, e.g., severe depression, should be summarized in this section. These analyses should be derived from both individual studies and from cross-study subset analyses.

Given the limited sample sizes in individual studies, analyses across multiple studies may be used to examine results in a subset of patients. These subset analyses should be carried out for major demographic (age, sex, race) and other intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, ethanol, tobacco, body weight). The limitations of such analyses, however, must be recognized (ICH E9).

The results of any bridging studies using clinical endpoint - for example to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)- should be summarised in this section. An analysis of the similarity of efficacy in subjects between regions should be summarized here. An independent subsection can be created to summarize these kinds of data.

3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data from pre-clinical studies, pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies that pertain to the dose-response or blood level-response relationship of effectiveness, the dose-blood level relationship, the method of dose selection, and choice of dose interval. For pharmacokinetic and pharmacodynamic studies from which data have been summarized in Section 2.3, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Section 2.3, without repeating the summaries.

Results and analysis of these studies should support the dosing recommendations proposed in labeling, including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualization of dosage. Any identified deviations from relatively simple dose-response or blood-level response relationships due to

non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose-response relationships that result from a patient's age, size, sex, disease, or other factors should be described. Any evidence of different pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in Section 2 may be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of test drug).

3.4.1 Evidence of Long-Term Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarized. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

Controlled studies specifically designed to collect long-term efficacy data should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects.

The effect of switching to other therapies upon assessment of long-term efficacy during the clinical trials should be discussed. Predefined switching criteria and the characteristics of the subjects who switched should be described for each treatment arm. Sufficient information should be given to allow assessment of the impact of these factors on the ultimate conclusions of the clinical trial. Similar considerations apply to any kind of rescue therapy. In the analysis of outcome (survival, major morbid events), data from subjects who switched to another therapy should be included in the data up to the time of the switch. After the subjects switch their data should be included in the intent-to-treat population in the assessment of the major clinical outcome. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see section 4).

Section 3 Appendix

Tabular presentations should be provided that summarise the most important results from all studies pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports (ICH-E3), and studies described in abbreviated reports). When more than one section 3 is provided for an application with more than one indication, usually each section should have its own appendix with tables.

Example tables are provided, but thought should be given to the use of these examples. These examples will not be precisely relevant to every application. Conversely, applications will generally require many other unique tables and/or figures that are not represented in these examples.

Applicants should note that it is not mandatory to use the example tabular formats provided in this guidance. Applicants are encouraged to modify the tabular formats as needed and provide the best possible presentation of information, in order to facilitate the understanding

and evaluation of the results. It is recognised that alternate formats may be necessary to ease preparation of an electronic document.

Table 3.1 Description of Clinical Efficacy and Safety Studies

Table 3.2 Results of Efficacy Studies

4. SUMMARY OF CLINICAL SAFETY

This section is a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports, and other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICH E3):

– The extent of exposure (dose, duration, number of patients, type of patients) should be examined as a determinant of the degree to which safety can be assessed from the database.

– The more common adverse events and changes in laboratory tests should be identified and classified in a reasonable fashion, and their analysis should be summarized.

– Serious adverse events (defined in ICH E2A) and other important adverse events (defined in ICH E3) should be identified and their analysis should be summarized.

Analysis of safety in subsets of the population (e.g. healthy subjects and patients, demographic) should be presented where appropriate.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, by appending a selection of descriptive tables and figures.

4.1 Exposure to the Drug

4.1.1 Overall Safety Evaluation Plan

The overall safety evaluation plan should be described briefly, including special considerations/observations concerning the preclinical data, any relevant pharmacological class effects, and how the overall clinical development programme was designed to evaluate safety.

4.1.2 Overall Extent of Exposure (Table 4.1)

A table (see example) and appropriate text should be generated that present the overall extent of drug exposure from all phases of the clinical study development programme. The table should indicate the numbers of subjects/patients exposed at various doses, routes, and durations. If a large number of different doses and/or durations of exposure were used, these may be grouped in a manner appropriate for the drug under review. Thus, for any dose or range of doses, duration of exposure can be summarized by the number of subjects/patients

exposed for specific periods of time, such as 1 day or less, 2 days to 1week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In some applications it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject/patient in this presentation could be the maximum dose received by that subject/patient, the dose with longest exposure, and/or the mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m^2 basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events of changes in laboratory variables.

It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics (Table 4.2) of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 [Studies in Support of Special Populations: Geriatrics] and ICH E11 [Clinical Investigation of Medicinal Products in the Paediatric Population].

In addition, one or more tables should show the relevant characteristics of patients, and the numbers of patients with special characteristics should be considered.

For example:

- Stage/severity of disease
- Hospitalized patients versus outpatients
- Impaired renal or hepatic function
- Patients taking particular medications
- Major geographical locations where studies were conducted
- Presence of concomitant illnesses (e.g., coronary artery disease, diabetes mellitus)

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

It should be noted that certain patients were excluded from studies (concomitant illness, severity of illness, concomitant medications).

Separate demographic tables should be provided for every indication, although closely related indication may be considered together. This is particularly important when the various indications involve patient populations with very different demographic characteristics, e.g., luteinising hormone releasing hormone analogues for prostatic cancer, endometriosis, and precocious puberty.

4.1.4 Description of Safety Studies Not Presented Elsewhere

Studies pertinent to the evaluation of efficacy will be listed in tables and have narrative summaries (including safety data) in Section 3. Any important safety studies not adequately described in tables or Section 3 should be briefly described here. For example, narrative descriptions of controlled studies to evaluate particular adverse events (sedation, sexual function, effects on driving, absence of a class adverse effect) or to assess safety in particular demographic subsets and narrative descriptions of uncontrolled safety trials would often not be included in Section 3 and should be presented here.

4.2 Adverse Events

4.2.1 Frequency of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in this section and the tables in the section 4 Appendix.

All new adverse events occurring after treatment has begun (including those not seen at baseline or that worsened during treatment) should be summarized in tables listing each event, the number of subjects/patients in whom the event occurred and the frequency of occurrence in subjects/patients treated with the drug under investigation, with comparator drugs, and with placebo. In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS, those not seen at baseline and those that worsened even if present at baseline). Such tables could also present results of other doses and could be modified to show, e.g., adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies, presentation of data by study will often suffice. Conversely, when the relevant exposure data is not concentrated in a small number of studies, it may be more appropriate to group the studies and pool the results to present an overall summary. Any study with an unusual adverse event pattern should be presented separately.

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from many studies, it is important to use standardized terms to describe events and collect synonymous terms under a single preferred term. This can be done with a standard dictionary, and the MedDRA terminology (ICH M1 guideline) should be used. Until MedDRA can be fully implemented, other dictionaries can be used, but must be specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help assess the clinical importance of adverse drug reactions (ADR). These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration).

4.2.2 Analyses of Adverse Events

4.2.2.1 Pooling Across Studies to Obtain Subject Sub-groups for Estimating and Comparing Incidence

4.2.2.1.1 General Considerations

Examination of less common adverse events that may not even occur in some studies is important in safety analysis. Pooling data from different studies is a method to improve the precision of incidence estimates, i.e., to narrow the confidence intervals and to decrease the influence of local factors. The larger sample available in a pooled analysis may also permit explorations for interactions in subgroups of the population, such as age, sex, race, concomitant illness, or concomitant drug use. Finally, a more general goal of pooling is to facilitate the generation of hypotheses about risk, some of which may become the focus of future studies that are more definitive.

Although pooling may be useful and appropriate, it should be approached with caution because interpretation can be difficult; it is more informative to acknowledge and display the variability and explain it.

The following issues should be considered in planning pooled analyses:

- It is most appropriate to combine data from studies that are of similar design, e.g., similar in dose, duration, methods of determining adverse events, and population.
- If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- The extent of analysis needed depends on the severity of the adverse event and the strength of evidence of drug causation.. Differences in rates of drug-related, serious events deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- Examination of which patients experience extreme laboratory value abnormalities may be useful in identifying subgroups of patients who are at particular risk for certain adverse events.

4.2.2.1.2 Methodology

If a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is most common to combine the numerator events and the denominators for the selected studies. Other more formal weighting methods are available, e.g., weighting studies on the basis of study size or inversely to their variance. If the goal of pooling is to increase the power to detect a difference between two treatment groups, e.g., drug vs. placebo, a test of heterogeneity, might be useful (ICH E9). Alternatively, a more informal evaluation can be used.

Groups of studies that could be used in pooled safety analyses include:

- All controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations).

These groupings are the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.

- All studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- All studies using a particular dose route or regimen, or a particular concomitant therapy.
- Studies in which adverse event reports are elicited by checklist or direct questioning or studies in which events are volunteered.
- Pools of studies by region.

It is almost always useful to carry out the first two groupings; the others chosen will vary from drug to drug and will be influenced by inspection of individual study results. Whatever methods are used, it should be recognized that, as for results of single studies, any numerical rate is a rough approximation.

4.2.2.2 Common Adverse Events

Tabular displays of adverse event rates in section 4 Appendix should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. Additionally, comparisons of rates of adverse events between treatment and control groups in individual trials should be summarized here.

It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to the following:

– dosage;
– mg/kg or mg/m^2 dose;
– dose regimen;
– duration of treatment;
– total dose;
– dosing schedule
– demographic characteristics such as age, sex, race
– concomitant medication use,
– other baseline features such as renal status;
– efficacy outcomes;
– drug concentration.

It may also be useful to summarize the results of examination of time of onset and duration for these drug-related events.

It is not intended that every adverse event be subjected to rigorous statistical evaluation of possible relationship to each of the above factors. It may be apparent from initial display and inspection of the data that a significant relation to demographic or other baseline features is not present. In that case, no further analysis of these particular factors is needed. Further, it is not intended that all such analyses performed be presented or summarized in this report. While the full

integrated analysis of safety that is submitted in some regions will contain details about all such analyses, this summary of human safety experience should summarize those analyses that yielded potentially important (positive or negative) information regarding the safety of the drug.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

4.2.2.3 Deaths

In general, all deaths occurring during the clinical programme, including the posttreatment follow-up period and deaths that may have resulted from a process that began during studies should be listed in a table in the section 4 Appendix (excepting only deaths that are clearly disease-related, in studies of conditios with high mortality such as advanced cancer, or studies where mortality from disease is a primary study endpoint). Deaths should be examined individually and analyzed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not informative but even a few cases of death due to QT prolongation-associated arrhythmias, aplastic anemia, or liver injury may be informative. Special caution is needed before an unusual death is attributed to concomitant illness.

4.2.2.4 Other Serious Adverse Events

Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or proceeding the deaths) should be displayed. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events by using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented.

4.2.2.5 Other Significant Adverse Events

Marked hematologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (withdrawal of test drug/investigational product treatment, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of drug treatment represent an important safety concern and deserve particular attention in the analysis of drug safety for two reasons. First, even for expected events (based on pharmacologic activity), the need to discontinue (or otherwise alter) treatment reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug-related event not yet recognized as drug related. Adverse events leading to withdrawals should be considered possibly drug-related even if this was not recognized initially and even if the event was thought to represent intercurrent illness. Rates of discontinuations should be compared across

studies and compared with those for placebo and/or active control treatment In addition, the study data should be examined for any evidence that specific patient features might increase the risk of these events (e.g., demographic characteristics, concomitant illnesses, dose of the drug, or particular concomitant treatments). Serious adverse events that occurred after the drug use was discontinued should be included in Section 4.2.2.4.

4.2.2.6 Narratives

The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as provided in individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, and should not usually be included here, unless an abbreviated narrative of particular events is critical to the assessment of the drug.

4.2.3 Integrated Analysis of Serious and Significant Events

Although deaths, other serious events, and other significant events are presented separately both in study reports and here, assessment of the causality and the cofactors for these events is often complicated by the fact that they are uncommon. As a result, consideration of the more important events as a group, and together with less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death may become much clearer when considered in the context of cases of syncope, palpitations, and asymptomatic arrhythmias.

Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Similarly, serious events should be examined for evidence of relationship to dose, and/or specific treatment regimens.

4.3 Clinical Laboratory Evaluations

This section describes changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention are reported in section 4.2.2. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The needed evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3).

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data comprise haematology, biochemistry, urinalysis and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, i.e., the group mean and median values,
- the range of values, and the number of subjects or patients with abnormal values or with abnormal values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centres with differences in

normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual patient changes by treatment group can be shown with a variety of approaches, including (ICH E3):

- "Shift tables" - These tables show the number of subjects/patients who are low, normal, or high at baseline and then at selected time intervals.
- Tables showing the number or fraction of patients who had a change in a value of a predetermined size at selected time intervals.
- A scatter graph comparing the initial value and the on-treatment values of a laboratory measurement for each patient. These displays identify outliers readily (it is useful to include patient identifiers for the outliers).

- Individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy).

4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

The manner of presenting cross-study observations and comparisons of vital signs (e.g., pulse, blood pressure, temperature, respiratory rate), weight and other data (e.g., electrocardiograms and X-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose-response or drug concentration-response relationship or relationship to patient variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events.

Any data pertinent to specific safety concerns that are collected (e.g., Holter monitoring QT interval prolongation, PK/PD studies, pharmacologic studies) should be presented separately. The events themselves (Torsade de pointes arrhythmias, syncopal events) would be presented as adverse events.

4.5 Safety in Special Patient Groups and Situations

4.5.1 Intrinsic Factors

This section should summarize safety data pertinent to individualising therapy or patient management on the basis of demographic and other intrinsic factors. Intrinsic factors (ICH E5) include age, sex, height, weight, lean body mass, genetics, body composition, other illness and organ dysfunction. Analysis of the impact of such factors on safety outcomes will have been shown in other sections but should be summaried here, together with pertinent PK or other information, e.g., in patients with renal or hepatic disease. If a sufficiently large number of patients with a given co-morbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the co-morbid condition affected the safety of the drug under study. Cross reference should be made to the tables or description of adverse events when analyses of such sub-groups has been carried out.

4.5.2 Extrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of extrinsic factors. Extrinsic factors (ICH E5) are factors associated with the patient environment. Examples are the medical environment, use of other drugs (see 5.3, Drug Interactions), use of tobacco, use of alcohol, and food habits.

For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by post-marketing experience, or by information on similar drugs, information should be provided here.

4.5.3 Drug- Interactions

Studies on potential drug-drug or drug-diet interactions are presented in the Clinical Pharmacology section of the dossier. Interactions with potential impact on safety should be summarized here, based on PK, PD, or clinical observations.

Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

4.5.4 Use in Pregnancy and Lactation

Any information on safety during pregnancy or breast-feeding that becomes available during clinical development or from other sources should be summarised here.

4.5.5 Overdose

All available information on overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarized and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

4.5.6 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be discussed and clearly cross-referenced to the preclinical summary. Particularly susceptible patient populations should be identified and recommendations justified.

If studies on abuse potential have not been performed for a drug that belongs to a class of drugs known to have abuse potential, , the reasons why studies are considered unnecessary should be discussed.

4.5.7 Withdrawal/Rebound

Any information or study results pertinent to rebound effects should be summarized and discussed. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Specific studies concerning withdrawal and/or rebound should be presented separately.

Data concerning tolerance should be presented under section 3, Summary of Clinical Efficacy.

4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, coordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarized. When specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability are performed, the results should be presented separately.

4.6 Post-marketing data

If the drug has already been marketed, details of the number of subjects estimated to have been exposed should be provided and categorised, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subject exposed should be described. If estimates of the demographic details are available from any source, these should be provided.

A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions.

Any post-marketing findings in subgroups should be described.

Section 4 Appendix

Tabular presentations should be provided that summarise the key results from all studies pertinent to the evaluation of safety.

Example tables are provided, but thought should be given to the use of these examples. These examples will not be precisely relevant to every application. Conversely, applications will generally require many other unique tables and/or figures that are not represented in these examples.

Applicants should note that it is not mandatory to use the example tabular formats provided in this guidance. Applicants are encouraged to modify the tabular formats as needed and provide the best possible presentation of information, in order to facilitate the understanding and evaluation of the results. It is recognised that alternate formats may be necessary to ease preparation of an electronic document.

See sections 4.2.1, 4.2.2.3, and 4.3 of this guidance for additional discussion regarding the content of section 4 tables.

Table 4.1 Patient Drug Exposure by Mean Daily Dose and Duration of Treatment

Table 4.2 Demographic Profile for Patient Studies with Test Product

Table 4.3 Treatment Emergent Adverse Event Incidence in the Largest Trials

Table 4.4 Patient Discontinuations by Study: Controlled Trials

Table 4.5 Deaths Listing

5. SYNOPSES OF INDIVIDUAL STUDIES

The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module V, followed by all individual study synopses organized in the same sequence as the study reports in Module V.

It is expected that one synopsis will be prepared per study for use in all regions, and the same synopsis will be used in this section and as part of the clinical study report in module V. The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important study may be longer, e.g. 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

Table 1.1

Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age(mean, range)	Mean Parameters (+/- SD)						Study Report Location
					Cmax (mg/L)	Tmax (hr)	AUC* (mg/L x hr)	Cmin* (mg/L)	T1/2 (hr)	CL (ml/min /kg)	
192 (Japan)	Pilot relative BA study comparing the absorption from a 200mg tablet batch to a 200mg reference batch.	Open, randomized, cross-over, single 200 mg dose	200mg Tab., p.o. [17762] 200mg Tab.. p.o. [19426]	20 (10/10) Healthy volunteer (27, 20-35)	83±21 80±32	1 0.5	217 ±20 223 ±19		3.1 2.9	5.08 ±14	1.52
195 (Japan)	Comparative BA study of xx under fasted and fed conditions	Open, randomized, cross-over, single dose	200mg Tab, p.o. [19426]	30 (15/15) Healthy volunteer 32 (26-50)	83 ±21 120 ±30	1 2	217 ±20 350 ±40				

AUC*: AUC_{TAU} or AUC_{inf}

Cmin**: For multiple dose studies

Table 1.2

Summary of *In Vitro* Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection times % Dissolved	Study Report Location
1821	979-03	25mg Cap.	Dissolution: Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium/Temperature: Water 37°	12	10 20 30 (min) 42 71 99 (%)	vol. 1.24

Table 2.1

Summary of PK Studies

Study/ Protocol # (Section 2.2.3 Country)	Product ID/Batch # (NME)	Study Objective	Study Design	# Subjects Completed/Entered (M/F)	HV/P (Age: Mean, range)	Treatments		Mean Pharmacokinetic Parameters (%CV) Substrate Drug					Mean ratio (Confidence interval)		Location (Vol. No., Page)
						Substrate	Interacting Drug	Cmax	Tmax	AUC	T1/2	CL/kg	Cmax	AUC	
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Randomized, Crossover	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Drug X 100 mg bid x 7d	Placebo	45 (18) Fg/mL	2.0 (30) hr	456 (24) Fg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.15 1.01-1.30	1.16 1.03-1.34	Vol. 35 Pages 1-300
						Drug X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) Fg/mL	2.1 (35) hr	530 (27) Fg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B batch 0034	Effect of drug X on warfarin	Randomized, Crossover	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Warfarin 10 mg qd x 7d	placebo	12 (25) Fg/mL	1.5 (30) hr	60 (37) Fg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.01 0.92-1.09	1.02 0.92-1.10	Vol. 35 Pages 1-300
						Warfarin 10 mg qd x 7d	drug X 100 mg bid x 7d	13 (20) Fg/mL	1.45 (27) hr	64 (39) Fg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			
002 (UK)	19B2 Batch 0035	Effect of Cimetidine on Drug X	Crossover, Single sequence	(4M/8F) (4M/8F)	HV (30, 19-45)	Drug X 50 mg bid x 5d	Placebo	49 (18) F/mL	2.1 (30) hr	470 (24) Fg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03-1.40	1.36 1.11-1.53	Vol. 36 Pages 1-240
						drug X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) Fg//mL	2.2 (30) hr	640 (24) Fg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

HV=Healthy Volunteers, P=Patients

Table 3.1

Description of Clinical Efficacy and Safety Studies

Study ID	PI location	Study start Study status	Design Control type	Study & Ctrl Drugs Dose,Route & Regimen	# subjs by arm entered/compl.	Gender M/F Age Range	Diagnosis Inclusion Criteria	Endpoints
PG- 2476	D. Smithl U. Siberia	Aug-94 Complete	Randomised Placebo	TP: 30 mg po bid Pbo	27/24 23/20	40/54 20-64 yrs	Mild hypertension Diastolic 90-100 Systolic 150-170	
PG- 2666	A.Jones U. Sicily	May-98 On-going	Parallel Dose-response	TP: 100 mg po bid TP: 50 mg po bid TP: 25 mg po bid TP: 10 mg po bid Placebo	34/30 30/28 34/32 26/20 28/26	20/34 24-68 yrs	Mild hypertension Systolic 150-170 Diastolic 90-100	

Table 3.2

Results of Efficacy Studies

Study	Treatment Arm	# Enrolled/Completed	Mean systolic and diastolic BP					Other Endpoints	
			Baseline	20 wks	40 wks	% improved**			
PG-2666	TP: 100 mg po bid	34/30	162/96	140/85	138/84	88			
	TP: 50 mg po bid	30/28	165/97	146/87	146/87	78			
	TP: 25 mg po bid	34/32	167/96	148/88	148/88	71			
	TP: 10 mg po bid	26/20	162/95	153/93	153/93	48			
	Placebo	28/26	166/97	160/92	159/91	30			

**Provide definition

Table 4.1

Patient Drug Exposure by Mean Daily Dose and Duration of Treatment[1,2]
N= Cutoff Date:

Duration (Weeks)	**Mean Daily Dose (mg)**							
	0 < Dose ≤ 5mg	5 < Dose ≤ 10mg	10 < Dose ≤ 20mg	20 < Dose ≤ 30mg	30 < Dose ≤ 50mg	50mg < Dose	Total (Any Dose)	Percent
0 < Dur ≤ 1								
1 < Dur ≤ 2								
2 < Dur ≤ 4								
4 < Dur ≤ 12								
12 < Dur ≤ 24								
24 < Dur ≤ 48								
48 < Dur ≤ 96								
96 < Dur								
Total (Any Duration)								
Percent								

[1] Similar tables can be calculated for median, for modal, and for maximum dose. The same table can be generated for any pool of studies and any subgroup of interest, e.g., on the basis of age, sex, ethnic factors, comorbid condition, concomitant medications, or any combination of these factors.

[2] Dose may also be expressed as mg/kg, mg/m^2, or in terms of plasma concentration if such data are available.

Table 4.2 **Demographic Profile for Patient Studies with Test Product** **Cutoff Date:**			
	Treatment Groups		
	Test Product N =	Placebo N =	Active Control N =
Age (years) Mean Range Groups <40 40 - 64 65 - 75 >75	 % % % %	 % % % %	 % % % %
Gender Female Male	% % %	 % %	 % %
Ethnicity Asian Black Caucasian	 % % %	 % % %	 % % %
Other Factors			

Table 4.3 **Treatment Emergent Adverse Event Incidence in the largest trials**								
	Reported incidence (%) by Treatment Groups							
Body System / Adverse Event	**Study 95-0403**			**Study 96-0011**		**Study 97-0007**		**Study 98-0102s**
Body as a whole	**Drug x 60 mg bid N =104**	**Drug x 30 mg bid N =102**	**Placebo N = 100**	**Drug x 60 mg bid N = 500**	**Placebo N=495**	**Drug x 60 mg bid N=200**	**Drug y 100 mg qd N=200**	**Drug x 60 mg bid N=800**
Headache								
Dizziness								
Etc.								
Cardiovascular								
Postural Hypotension								
Etc.								
Gastrointestinal								
Constipation								

Table 4.4

Patient Withdrawals1 by Study: Controlled Trials

Cutoff Date:

Studies		**Total Withdrawal**	**Reason for Withdrawal**		
		N (%)	Adverse Events N (%)	Lack of Efficacy N (%)	Other N (%)
Study XXX	Drug X				
	Placebo				
Study AAA	Drug X				
	Comparator A				
Study BBB	Drug X				
	Comparator B				
Study CCC	Drug X				
	Comparator C				
All Trials					

1 Withdrawals are subjects who were enrolled but did not complete the study (includes subjects who discontinued treatment or changed to a different treatment prematurely and/or were lost to follow-up)

Table 4.5 **Deaths Listing**[1,2] **Treatment = Test Product** **Cutoff Date:**								
Trial	**Center**	**Patient**	**Age (yrs)**	**Sex**	**Dose (mg)**	**Time (Days)**	**Source**[3]	**Description**

1 A footnote should describe the rule for including deaths in the table, e.g., all deaths that occurred during a period of drug exposure or within a period of up to 30 days following discontinuation from drug and also those occurring later but resulting from adverse events that had an onset during exposure or during the 30 day follow up period. Other rules may be equally appropriate.

2 Similar lists should be provided for patients exposed to placebo and active control drugs.

3 This listing should include all deaths meeting the inclusion rule, whether arising from a clinical trial or from any secondary source, e.g., postmarking experience. The source should be identified in this column, i.e., 1^0 for deaths arising from primary source clinical trials and 2^0 for those arising from secondary sources.

MODULE V – CLINICAL STUDY REPORTS

Organisation of Clinical Study Reports and Related Information

Preamble

Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). This document provides guidance on the organisation of these study reports and other clinical data within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.

This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical data reports that are in the application.

The organization of clinical data within a CTD for the registration of new pharmaceuticals has been addressed here. With appropriate modifications, this organisation may also be applied to other types of applications presenting clinical data.

Organization of Clinical Study Reports and Related Information in Module V (Clinical) of The Common Technical Document (CTD)

July 20, 2000

A. Table of Contents of Clinical Study Reports and Related Information

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C. Clinical Study Reports

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   - 1.1 BA Study Reports
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   - 1.3 In Vitro-In Vivo Comparison Study Reports
   - 1.4 Reports of Bioanalytical and Analytical Methods
2. Reports of Studies Using Human Biomaterials Pertinent to Absorption or Disposition
   - 2.1 Plasma Protein Binding Study Reports
   - 2.2 Reports of Hepatic Metabolism and Interaction Studies
   - 2.3 Reports of Studies Using Other Human Biomaterials
3. Reports of Human Pharmacokinetic (PK) Studies
   - 3.1 Healthy Subject PK and Initial Tolerability Study Reports
   - 3.2 Patient PK and Initial Tolerability Study Reports
   - 3.3 Intrinsic Factor PK Study Reports
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4. Reports of Human Pharmacodynamic (PD) Studies

   4.1 Healthy Subject PD and PK/PD Study Reports

   4.2 Patient PD and PK/PD Study Reports

5. Reports of Efficacy and Safety Studies

   5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

   5.2 Study Reports of Uncontrolled Clinical Studies

   5.3 Reports of Analyses of Data From More Than One Study

   5.4 Other Study Reports

6. Reports of Post-Marketing Experience

7. Case Report Forms and Individual Patient Listings

Guideline on Organisation of Clinical Study Reports and Related Information in Module V (Clinical) of The Common Technical Document (CTD)

July 20, 2000

This guideline suggests a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

A Table of Contents for Study Reports

A Table of Contents for the study reports should be provided.

B. Tabular Listing of All Clinical Studies

A tabular listing of all human studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information may be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section C below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

C. Clinical Study Reports

1. Reports of BA and BE Studies

BA and BE studies evaluate the rate and extent of release of the active substance from the medicinal product. BA/BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose

of a study is to assess the PK of a drug, but also includes BA or BE information, the study report should be submitted in Section 3, and referenced in Sections 1.1 and/or 1.2.

Section 1.1 BA Study Reports

BA studies in this section include 1) studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously (absolute BA study) or as an oral liquid dosage form (relative BA study), 2) dosage form proportionality studies, and 3) food-effect studies.

Section 1.2 BE Study Reports

BE studies in this section compare the rate and extent of release of the drug substance from drug products (e.g., tablet to tablet, tablet to capsule). BE studies may include comparisons between 1) the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, 2) the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and 3) similar drug products from different manufacturers.

Section 1.3 In Vitro – In Vivo Comparison Study Reports

In vitro dissolution studies that provide BA/BE information, including studies used in seeking to correlate in vitro data with in vivo comparisons, should be placed in Section 1.3. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

Section 1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Section 1.4 and referenced in the appropriate individual study reports.

2. Reports of Studies Using Human Biomaterials Pertinent to Absorption or Disposition

Human biomaterials is a term that refers to proteins, cells, and tissues derived from human sources that are used in vitro or ex vivo to assess absorption and disposition properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways relative to drug absorption and elimination and to assess bi-directional drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section.

Section 2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided in Section 2.1. Protein binding data from PK blood and/or plasma studies should be provided in Section 3.

Section 2.2 Reports of Hepatic Metabolism and Interaction Studies

Reports of metabolic/interaction studies with hepatic tissue should be placed in Section 2.2.

Section 2.3 Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in section 2.3.

3. Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s).

The PK studies in Sections 3.1 and 3.2 generally (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Section 3.1 to 3.2, as appropriate. These studies characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Sections 3.1 and/or 3.2. Apart from describing mean PK in normal and patient volunteers, PK studies also describe the range of individual variability. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors which may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organized in Sections 3.3 and 3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during efficacy and safety studies can also address questions about intrinsic and extrinsic factors contributing to the variability in the dose-exposure-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 3.5.

Section 3.1 Healthy Subject PK and Initial Tolerability Study Reports

Study reports of PK and initial tolerability in healthy subjects should be placed in Section 3.1.

Section 3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK studies and initial tolerability in patients should be placed in Section 3.2.

Section 3.3 Intrinsic Factor PK Study Reports

PK study reports to assess intrinsic factors, such as age, race and gender, should be placed in Section 3.3.

Section 3.4: Extrinsic Factor PK Study Reports

PK studies to assess extrinsic factors, such as other drugs, food, or smoking, should be placed in Section 3.4.

Section 3.5: Population PK Study Reports

Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 3.5.

4. Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the effects of a drug product in humans, as opposed to those studies whose primary objective is to establish efficacy or to accumulate safety data (see Section 5), should be placed in Section 4.

PD studies in Section 4 thus should include 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the main clinical effect, and 3) studies of other properties not related to the desired clinical effect, including studies to focus on specific safety concerns, e.g., QTc prolongation. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected together with drug concentration information (concentration-response or PK/PD studies). Relationships between PK and PD data may generally be evaluated using an appropriate model that can be used as a basis for interpolation and/or extrapolation of dose- and/or concentration-response information.

Dose-finding and/or PK-PD studies may be conducted in healthy subjects and/or patients, and may also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of PD, dose-finding, and/or PK/PD studies conducted in healthy subjects should be placed in Section 4.1, and the reports for those studies conducted in patients should be placed in Section 4.2.

In some cases, the PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). When these studies are part of the efficacy demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5, not in Section 4.

Section 4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in Section 4.1.

Section 4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in Section 4.2.

5. Reports of Efficacy and Safety Studies

Section 5 should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor or otherwise available, including both completed and ongoing studies of the drug in proposed and related indications, and, where appropriate, studies of indications other than those proposed. The study reports should provide the level of detail appropriate to the study. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see E3 and individual guidance by region).

Within Section 5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E-3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should come last.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it is included in the appropriate Section 5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5 and referenced as necessary in other Sections 5, e.g., Section 5A, Section 5B.

5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for the proposed use, should be included in Section 5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.1. The sequence in which studies were conducted is not pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Section 5.1. Controlled safety studies should also be reported in Section 5.1.

5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.2.

5.3 Reports of Analyses of Data from More than One Study

Clinical issues in an application may be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Section 5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications.

5.4 Other Study Reports

This section may include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports not included in Section 5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.1
- Reports of ongoing studies

6. Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in Section 6.

7. Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline. When these are submitted, they should be included in Section 7 and placed in the same order as the clinical study reports and indexed by study.

Table 1. Listing of Clinical Studies

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Number of Subjects**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	20	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	32	Cross-over	Two tablet formulations, 50 mg, oral	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	50	Cross-over	Tablet, 50mg single dose, oral	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	24	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	300	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	Patients with primary hypertension	48 weeks	Complete; Full